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February 10, 1999

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APPLICATION NUMBER: ***60/071,023***
FILING DATE: ***January 13, 1998***

PRIORITY DOCUMENT

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DOCKET NUMBER
2933152USP1

CERTIFICATE UNDER 37 CFR 1.10:
"Express Mail" mailing label number: EM422750320US
Date of Deposit: January 13, 1998

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By: _____
Name: Bil Smith

REQUEST FOR PROVISIONAL APPLICATION UNDER 37 C.F.R. § 1.53(b)(2)

BOX PROVISIONAL PATENT APPLICATION
Assistant Commissioner for Patents
Washington, DC 20231

Sir:

This is a request for filing a Provisional application for patent under 37 CFR § 1.53(b)(2) entitled A METHOD OF ENHANCING CANCER THERAPY by the following inventor(s):

Full Name Of Inventor	**Family Name** Paterson	**First Given Name** I.	**Second Given Name** Alick
Residence & Citizenship	**City** Saskatoon	**State or Foreign Country** Canada	**Country of Citizenship** United Kingdom
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1. ☒ Enclosed is the Provisional application for patent as follows: 19 pages of specification, claims and abstract, and 3 sheets of drawings.

2. ☐ A Verified Statement that this filing is by a small entity (37 CFR 1.9, 1.27, 1.28) is attached.

3. ☒ Payment of Provisional filing fee under 37 C.F.R. § 1.16(k) :
   - ☐ Attached is a check in the amount of $.
   - ☒ Please charge Deposit Account No. 13-2725.
   - ☐ PAYMENT OF THE FILING FEE IS BEING DEFERRED.

4. ☒ The Commissioner is hereby authorized to charge any additional fees as set forth in 37 CFR §§ 1.16 to 1.18 which may be required by this paper or credit any overpayment to Account No. 13-2725.

5. ☐ Enclosed is an Assignment of the invention to , Recordation Form Cover Sheet and a check for $ to cover the Recordation Fee.

6. ☐ Also Enclosed:

7. ☐ The invention was made by the following agency of the United States Government or under a contract with the following agency of the United States Government:

8. ☒ Address all future communications to the **Attention of Douglas P. Mueller** (may only be completed by attorney or agent of record) at the address below.

9. ☒ A return postcard is enclosed.

Respectfully submitted,

Paterson et al

By their Attorneys,

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90 South Seventh Street
Minneapolis, Minnesota 55402
(612) 332-5300

Dated: January 13, 1998

By _____
Douglas P. Mueller
Reg No. 30,300
DPM:vvh

B&P File No. 10242-001/MG

Title: A Method of Enhancing Cancer Therapy

FIELD OF THE INVENTION

The present invention relates to a method for enhancing cancer therapy by administering an effective amount of an antineoplastic modulator. Preferred antineoplastic modulators are propargylamines including aliphatic propargylamines and aromatic propargylamines. The invention also includes a pharmaceutical composition for enhancing the treatment of cancer comprising an effective amount of an antineoplastic modulator of the present invention in admixture with a suitable diluent or carrier.

BACKGROUND OF THE INVENTION

Cancer is a collection of diseases involving inappropriate and unregulated growth of cells in the body. The aim of chemical therapy of cancer is to introduce a chemical (antineoplastic drug) which will kill the cancerous cells but will not damage normal cells. Conventional antineoplastic drugs act selectively on cells undergoing cell division, with the strategy that cancerous cells are dividing more rapidly than normal cells in the body. This poor selectivity, however, leads to severe side effects in cancer chemotherapy. The development of multi-drug resistance by cancerous cells makes many cancers unresponsive to chemotherapy and therefore incurable.

An antineoplastic modulator is a chemical which modifies the action of an antineoplastic drug, improving the selectivity, and therefore efficacy of the antineoplastic drug. An antineoplastic modulator acts to protect non-cancerous tissue from the toxic effects of the antineoplastic drug, to increase the ability of the antineoplastic drug to kill cancerous cells, and to suppress the multi-drug resistance exhibited by many cancerous cells.

The present inventors have prepared many novel propargylamines as described in United States Patent No. 5,169,868. The inventors have shown that the novel propargylamines are useful as MAO-B

inhibitors and are useful in treating various neuropsychiatric disorders including Parkinson's disease, Alzheimer's disease, depression, attention deficit disorder, hyperactive disorders as well as other aging-associated diseases.

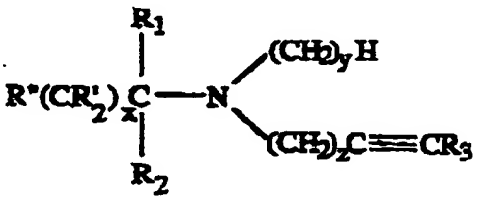
The present inventors have surprisingly found that the propargylamines are also useful as antineoplastic modulators and can enhance the effect of antineoplastic drugs.

SUMMARY OF THE INVENTION

Broadly stated, the present invention relates to a method of enhancing cancer therapy by administering an effective amount of a propargylamine. The present inventors have shown that propargylamines enhance the killing of tumor cells by antineoplastic drugs and protect normal cells from the cytotoxic effects of antineoplastic drugs. Consequently, propargylamines are well-suited to enhance any chemotherapy regime and can increase the effectiveness while reducing the side-effects of cancer therapy.

In one aspect, the present invention relates to a method for enhancing the effect of an antineoplastic drug comprising administering an effective amount of a propargylamine to an animal in need thereof.

In one embodiment, the propargylamine is of the general formula I



wherein

x is an integer ranging from 0 to 13;

y is an integer ranging from 0 to 5;

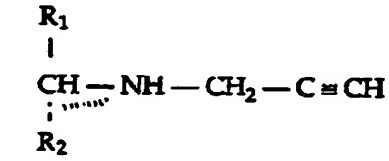
z is an integer ranging from 0 to 5;

R_1, R_2 and R_3 are the same or different and represent hydrogen or a straight chain or branched lower alkyl; and

R^1 and R^{11} are the same or different and represent hydrogen or a halogen and pharmaceutically acceptable salts thereof.

Preferably the lower alkyl has between 1 and 4 carbon atoms and the halogen atom is selected from fluorine, chlorine, bromine and iodine. More preferably, the lower alkyl is selected from methyl.

In another embodiment, the propargylamine is of the general formula II:

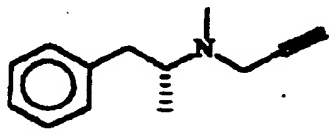


wherein:

R^1 is hydrogen or CH_3;

R^2 is $(CH_2)_nCH_3$ where n is 0 or an integer from 1 to 16, preferably 1 to 10, more preferably 1 to 5, and the pharmaceutically acceptable salts thereof.

In a further embodiment, the propargylamine is R-deprenyl having the following formula III:



In another embodiment, the propargylamine is R-desmethyldeprenyl having the following formula IV:

In yet another embodiment, the propargylamine is Rasagiline having the following formula V:

In another aspect, the present invention relates to a method of increasing the sensitivity of a tumor to an antineoplastic drug comprising administering an effective amount of propargylamine to an animal in need thereof. The propargylamine may be of a general formula I, II, III, IV or V as described hereinabove.

In a further aspect, the present invention provides a method of protecting normal cells from the cytotoxic effects of an antineoplastic drug comprising administering an effective amount of a propargylamine to an animal in need thereof. Preferably, the propargylamine is of the general formula I, II, III, IV or V as described hereinabove.

In a further aspect, the present invention relates to a method for treating cancer comprising administering an antineoplastic drug and an effective amount of a propargylamine to an animal in need thereof. Preferably, the propargylamine is of the general formula I, II, III, IV or V as described hereinabove.

The present invention also includes a pharmaceutical composition useful for enhancing cancer therapy comprising an effective amount of a propargylamine in admixture with a suitable diluent or carrier.

The pharmaceutical compositions of the present invention may be useful in enhancing the activity of an antineoplastic drug or increasing the sensitivity of a tumor to an antineoplastic drug.

The present invention also includes a pharmaceutical composition useful for treating cancer comprising an antineoplastic drug and an effective amount of a propargylamine of the present invention.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described in relation to the drawings in which:

Figure 1 is graph showing the RATIO of various antineoplastic modulators versus the concentration of the antineoplastic modulator.

Figure 2 is a graph showing the relative cell survival of normal bone marrow versus time, in the presence of various modulators.

Figure 3 is a graph showing the relative cell survival of cancer cells versus time, in the presence of various modulators.

DETAILED DESCRIPTION OF THE INVENTION

Broadly stated, the present invention relates to a method of enhancing cancer therapy by administering an effective amount of a propargylamine. The present inventors have shown that propargylamines enhance the killing of tumor cells by antineoplastic drugs and protect normal cells from the cytotoxic effects of antineoplastic drugs. Consequently, propargylamines are well-suited to enhance any chemotherapy regime.

In one aspect, the present invention relates to a method for enhancing the effect of an antineoplastic drug comprising administering an effective amount of a propargylamine to an animal in need thereof.

The term "effective amount" as used herein means an amount effective, at dosages and for periods of time necessary to achieve the desired result.

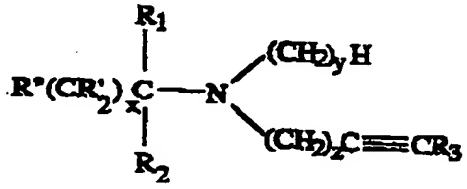
The term "animal" as used herein means any member of the animal kingdom including all mammals, birds, fish, reptiles and amphibians. Preferably, the animal to be treated is a mammal, more preferably a human.

The propargylamines (or "modulators") of the invention can be used to enhance the treatment of various forms of malignant diseases such as leukemias, lymphomas (Hodgkins and non-Hodgkins), plasmacytomas, histiocytomas, melanomas, adenomas, sarcomas, carcinomas of solid tissues, hypoxic tumours, squamous cell carcinomas, genitourinary cancers such as cervical and bladder cancer, hematopoietic cancers, head and neck cancers, and nervous system cancers. Treatment with the modulators may allow for treatment of tumors that are resistant to chemotherapy such as multi-drug resistant (MDR) tumor cells. MDR tumors include adenocarcinomas, neuroblastoma cells, leukemias, lymphomas, breast cancer and ovarian cancer cells. Treatment with the modulators may also allow for more effective radiotherapy of tumours that currently respond poorly to radiotherapy such as adenocarcinomas of the bowel and lung.

The antineoplastic drugs which may be potentiated or enhanced by the modulators include all chemotherapeutic agents such as cytosine arabinoside, cisplatinum, cyclophospamide, adriamycin, daunomycin, 5-fluorouracil, melphalan, CCNU i.e. 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosurca, chlorambucil, doxorubicin, carmustine, bleomycin sulfate, daunorubicin, dacarbazine, mitomycin, mitoxantrone hydrochloride, etoposide, streptozocin and taxol and taxol derivatives.

The propargylamines of the invention may be administered before, after and/or concurrently with the antineoplastic drug.

In one embodiment, the propargylamine is of the general formula I



wherein

x is an integer ranging from 0 to 13;

y is an integer ranging from 0 to 5;

z is an integer ranging from 0 to 5;

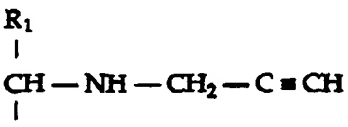
R_1, R_2 and R_3 are the same or different and represent hydrogen or a straight chain or branched lower alkyl; and

R^1 and R^{11} are the same or different and represent hydrogen or a halogen and pharmaceutically acceptable salts thereof.

Preferably the lower alkyl has between 1 and 4 carbon atoms and the halogen atom is selected from fluorine, chlorine, bromine and iodine. More preferably, the lower alkyl is selected from methyl.

Preferred propargylamines of the formula I are 2-heptyl-methyl propargylamine (2 HMP) and 2-heptyl-propargylamine (2 HPA).

In another embodiment, the propargylamine is of the general formula II:



wherein:

R^1 is hydrogen or CH_3;

R^2 is $(CH_2)_nCH_3$ where n is 0 or an integer from 1 to 16, preferably 1 to 10, more preferably 1 to 5, provided that is n is 0 then R^1 is not hydrogen,

and the pharmaceutically acceptable salts thereof.

Preferred compounds of the formula II include:

N-(1-Propyl) propargylamine;

N-(2-Propyl) propargylamine;

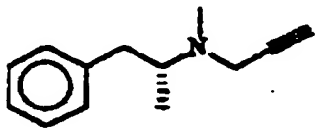
N-(1-Butyl) propargylamine;

N-(1-Pentyl) propargylamine;

N-(1-Hexyl) propargylamine;
N-(1-Heptyl) propargylamine;
N-(1-Octyl) propargylamine;
N-(1-Nonyl) propargylamine;
N-(1-Decyl) propargylamine;
N-(1-Undecyl) propargylamine;
N-(1-Dodecyl) propargylamine;
(R)-N-(2-Butyl) propargylamine (R-2BuPA);
(R)-N-(2-Pentyl) propargylamine;
(R)-N-(2-Hexyl) propargylamine;
(R)-N-(2-Heptyl) propargylamine;
(R)-N-(2-Octyl) propargylamine;
(R)-N-(2-Octyl) propargylamine;
(R)-N-(2-Decyl) propargylamine;
(R)-N-(2-Undecyl) propargylamine; and
(R)-N-(2-Dodecyl) propargylamine.

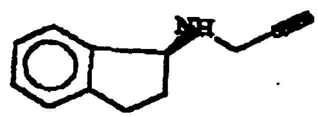
The preferred propargylamines of the chiral compounds formula I or II are the R-enantiomers.

In a further embodiment, the propargylamine is R-deprenyl having the following formula III:



In another embodiment, the propargylamine is R-desmethyldeprenyl having the following formula IV:

In yet another embodiment, the propargylamine is Rasagiline having the following formula V:



In another aspect, the present invention relates to a method of increasing the sensitivity of a tumor to an antineoplastic drug comprising administering an effective amount of propargylamine to an animal in need thereof. The tumor may be one that is resistant to cancer therapy such as a multidrug resistant tumor or a radioresistant tumor. The propargylamine may be of a general formula I, II, III, IV or V as described hereinabove.

In a further aspect, the present invention provides a method of protecting normal cells from the cytotoxic effects of an antineoplastic drug comprising administering an effective amount of a propargylamine to an animal in need thereof. Preferably, the propargylamine is of the general formula I, II, III, IV or V as described hereinabove.

In a further aspect, the present invention relates to a method for treating cancer comprising administering an antineoplastic drug and an effective amount of a propargylamine to an animal in need thereof. Preferably, the propargylamine is of the general formula I, II, III, IV or V as described hereinabove.

The propargylamines of the present invention may be prepared using techniques known in the art. For example, the aliphatic propargylamines may be prepared as described in the inventors United States Patent No. 5,169,868 which is incorporated herein by reference in its entirety. Briefly, the compounds may be prepared by condensing an alkyl bromide with N-methylpropylgylomine in the presence of a base and recovering the desired compound. Preferably the R-enantiomers are prepared.

The propargylamines of the invention may be incorporated into a pharmaceutical composition which may be useful in enhancing the activity of an antineoplastic drug or increasing the sensitivity of a tumor to an antineoplastic drug. The pharmaceutical composition may additionally include an antineoplastic drug and may be useful for treating cancer.

The pharmaceutical compositions of the invention can be prepared by per se known methods for the preparation of pharmaceutically acceptable compositions which can be administered to patients, and such that an effective quantity of the active substance is combined in a mixture with a pharmaceutically acceptable vehicle. Suitable vehicles are described, for example, in Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., USA 1985).

The pharmaceutical compositions of the invention can be for oral, topical, rectal, parenteral, local, inhalant or intracerebral use. They may be in solid or semisolid form, for example pills, tablets, creams, gelatin capsules, capsules, suppositories, soft gelatin capsules, gels, membranes, tubelets. For parenteral and intracerebral uses, those forms for intramuscular or subcutaneous administration can be used, or forms for infusion or intravenous or intracerebral injection can be used, and can therefore be prepared as solutions of the active compounds or as powders of the active compounds to be mixed with one or more pharmaceutically acceptable excipients or diluents, suitable for the aforesaid uses and with an osmolarity which is compatible with the physiological fluids. For local use, those preparations in the form of creams or ointments for topical use or in the form of sprays should be considered; for inhalant uses, preparations in the form of sprays, for example nose sprays, should be considered. Dosages to be administered depend on individual needs, on the desired effect and on the chosen route of administration, but daily dosages to humans by subcutaneous, intramuscular or intracerebral injection generally vary between about 1 ng and 1000 mg of active substance per Kg body weight, preferably between 1 ng and 10 mg per Kg body weight.

Other objects, features and advantages of the present invention will become apparent from the following. It should be understood, however, that disclosure and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this .

The following non-limiting examples are illustrative of the present invention:

EXAMPLES

EXAMPLE 1

***In Vitro* Protocol for Assessing the Capacity of Various Compounds to Modulate Cisplatinum Toxicity**

This protocol can be used for any normal/tumorigenic cell pair which will attach to plastic. Non-adherent lines (most tumor cells) require quantitation in soft agar. The experiments in question are based on rat2 cells, an established rat fibroblast line and a tumorigenic derivative thereof, NW16 cells, which are rat2 cells transformed by a Fujinami sarcoma virus oncogene (see work of Tony Pawson and $P130^{gag\text{-}fps}$). Rat2 cells are maintained in a sub-confluent randomly-proliferating state in Dulbecco's modified minimal essential media with 10% (vol/vol) calf serum in plates incubated at 37°C in a humidified CO_2 (10%) incubator. All experiments reported rely on clonogenic cell survival assays, performed as follows: cells are exposed, in 10 cm culture dishes, to various drugs in media plus serum for varying lengths of time; seeding is at varying cell numbers, over $\log_{10}$ ranges, depending upon the degree of killing anticipated. [For the figure presented, incubation was for 72 hours prior to washing and assessment of clonogenic survival]. Both control and the experimental cultures are then gently washed, twice, with phosphate buffered saline, then once more with media minus serum, and then left in media plus serum, undisturbed until macroscopic colonies appear (7-9 days of incubation). The colonies are then

fixed and stained with saturated methylene blue in 50% methanol and counted. The number of colonies, evaluated from 2 or more sets of duplicate cultures seeded at initial densities differing by factors of 10, are determined and converted to relative number of colonies, using the 0-hour control value as 1.0.

Presentation of Results by "RATIO" Method

A simplified presentation of the data, by the RATIO method, is show in Figure 1. By dividing the relative cell survival (R.C.S.) value obtained in cultures which have been exposed to the combination of anticancer drug (in this case, cisplatinum) and modulator by the corresponding R.C.S. value obtained for the anticancer drug alone reveals both the nature and the magnitude of the effect mediated by the modulator. Ratios greater than unity indicate that the modulator has conferred a protective response, whereas ratios less than unity indicate an enhanced cell killing.

Results

As can be seen from Figure 1, R- 2-heptyl-propargylamine (R-2 HPA), the desmethyl metabolite of R-2-heptyl-methyl propargylamine (R-2HMP) and R-2HMP (the pro-drug) are effective, over a wide concentration range (10^{7} - 10^{15} M), at protecting normal fibroblasts which are p53 dependent. R-2HPA is the more potent. R-Deprenyl whilst active, is less efficacious over a more limited concentration range (10^{-7} - 10^{-13} M). The usually inactive pro-drug isomer (+)2HMP is also inactive in this assay. In the tumorigenic cells (mutants in which p53 is absent) it can be seen that enhanced killing by cisplatinum occurs in the rang (10^{-11} - 10^{-15} M) but with a reversal to a protective effect when the concentration of R-2HMP is 10^{-9}M or greater.

Summary

R-2HMP and R-2HPA both protect normal cells and enhance the killing of tumor cells in the presence of cisplatinum in this *in vitro* fibroblast model. The protection and the enhanced killing occur in the 10^{-11}

- 10^{-15} M range. R-Deprenyl was also effective over a m re limited concentration, in the 10^{-7} to 10^{-13} M range. Since L-histidinol exhibits similar properties (although higher doses are required) in this and several other *in vitro* and *in vivo* paradigms, and in the presence of other anticancer drugs, it seems likely that R-2HMP, R-2HPA and the other aliphatic propargylamines, by analogy, will also exhibit activity in these other systems.

EXAMPLE 2

***In Vivo* Assessment of Anticancer Drug Modulators: Effects of R-2HPA**

Seven groups of mice were treated and assessed in this model.

1. nil control (1 mouse)
2. P388 control (1 mouse)
3. cisplatin (5 mice)
4. Histidinol (2 mice)
5. Histidinol + cisplatin (5 mice)
6. R-2HPA (4 mice)
7. R-2HPA + cisplatin (5 mice)

P388 cells (1 million) were injected into the tail vein of 22 female DBA/2J mice. The mice were then randomly divided into the above groups and injected (ip) with drugs 96h later. Doses were cisplatin 0.2 mg at 0 hour; Histidinol 5 mg/injection and R-2HPA 0.38 ug/injection; administered 5 time at -2, 0, +2, +4, and +6 hours. 48 h after drug treatment, cells from the femurs of the mice were harvested, washed and plated (at log10 dilutions) so as to allow quantitative and specific relative cell survival values to be generated for the responses of normal femoral bone marrow cells (specifically, CFU-C/GM or granulocyte/macrophage precursor cells) and clonogenic P388 leukemia cells.

As can be seen in Figure 2, both histidinol and R-2HPA were effective at protecting healthy bone marrow cells, whereas in Figure 3, it can be seen that both histidinol and R-2HPA enhanced the killing by cisplatin of P388 cells. It should be emphasized that the P388 leukemic line is

substantially resistant to the cisplatin (relative to the responses of the CFU-c/GM cells). In other words, both histidinol and R-2HPA are circumventing a profound drug-resistance trait *in vivo*. It can also be seen that this effect is obtained with R-2HPA at the low dose of 0.38 ug, producing a therapeutic index of about 50,000 between the protection of healthy normal cells and the killing of the cancerous cells. This effect is known to be p53 dependent vis a vis histidinol and it is likely to be the same with R-2HPA.

While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed examples. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

WE CLAIM:

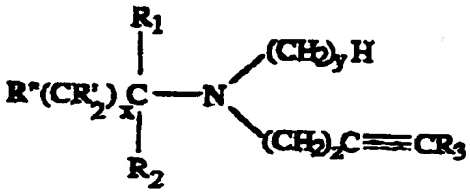
1. A method for enhancing the activity of an antineoplastic drug comprising administering an effective amount of a propargylamine to an animal in need thereof.

2. A method for increasing the sensitivity of a tumor to an antineoplastic drug comprising administering an effective amount of a propargylamine to an animal in need thereof.

3. A method according to claim 2 wherein the tumor is a drug resistant tumor.

4. A method of protecting normal cells form the cytotoxic effects of an antineoplastic drug comprising administering an effective amount of a propargylamine to an animal in need thereof.

5. A method according to any one of claims 1 to 4, wherein the propargylamine is of the general formula I



wherein

x is an integer ranging from 0 to 13;

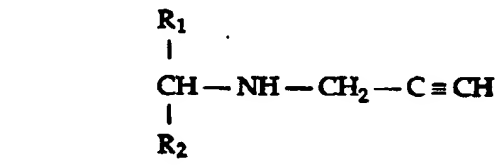
y is an integer ranging from 0 to 5;

z is an integer ranging from 0 to 5;

R_1, R_2 and R_3 are the same or different and represent hydrogen or a straight chain or branched lower alkyl; and

R^1 and R^{11} are the same or different and represent hydrogen or a halogen and pharmaceutically acceptable salts thereof.

6. A method according to any one of claims 1 to 4, wherein the propargylamine is of the general formula II:



wherein:

R^1 is hydrogen or CH_3;

R^2 is $(CH_2)_nCH_3$ where n is 0 or an integer from 1 to 16, preferably 1 to 10, more preferably 1 to 5, and the pharmaceutically acceptable salts thereof.

7. A method according to any one of claims 1 to 4, wherein the propargylamine is 2-heptyl-methyl propargylamine (2 HMP) or 2-heptyl-propargylamine (2 HPA).

8. A method according to any one of claims 1 to 4, wherein the propargylamine is R-deprenyl.

9. A method according to any one of claims 1 to 4, wherein the propargylamine is R-desmethyldeprenyl.

10. A method according to any one of claims 1 to 4, wherein the propargylamine is Rasagiline.

11. A method according to any one of claims 1 to 4, wherein the animal is a human.

12. A method for treating cancer comprising administering an antineoplastic drug and an effective amount of a propargylamine to an animal in need thereof.

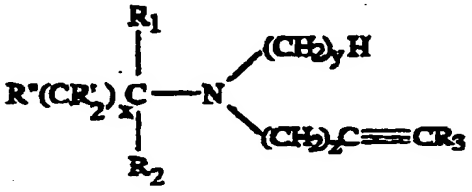
13. A method according to claim 12, wherein the antineoplastic drug is selected from the group consisting of cytosine arabinoside, cis-platinum, cyclophospamide, adriamycin, daunomycin, and 5-fluorouracil.

14. A pharmaceutical composition for enhancing the activity of an antineoplastic drug comprising an effective amount of a propargylamine in admixture with a suitable diluent or carrier.

15. A pharmaceutical composition for protecting normal cells from the cytotoxic effects of an antineoplastic drug comprising an effective amount of a propargylamine in admixture with a suitable diluent or carrier.

16. A pharmaceutical composition for treating cancer comprising an antineoplastic drug and an effective amount of a propargylamine.

17. A pharmaceutical composition according to claim 14, 15 or 16, wherein the propargylamine is of the general formula I:



wherein

x is an integer ranging from 0 to 13;

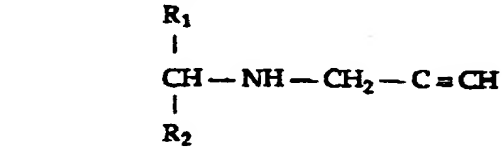
y is an integer ranging from 0 to 5;

z is an integer ranging from 0 to 5;

R_1, R_2 and R_3 are the same or different and represent hydrogen or a straight chain or branched lower alkyl; and

R^1 and R^{11} are the same or different and represent hydrogen or a halogen and pharmaceutically acceptable salts thereof.

18. A pharmaceutical composition according to claim 14 or 15, wherein the propargylamine is of the general formula II:



wherein:

R^1 is hydrogen or CH_3;

R^2 is $(CH_2)_nCH_3$ where n is 0 or an integer from 1 to 16, preferably 1 to 10, more preferably 1 to 5, and the pharmaceutically acceptable salts thereof.

19. A pharmaceutical composition according to claim 14, 15 or 16, wherein the propargylamine is R-deprenyl.

20. A pharmaceutical composition according to claim 14, 15 or 16, wherein the propargylamine is R-desmethyldeprenyl.

21. A pharmaceutical composition according to claim 14, 15 or 16, wherein the propargylamine is Rasagiline.

ABSTRACT OF THE DISCLOSURE

Antineoplastic drug modulators are described. The modulators are propargylamines which can enhance the cytotoxic effects of antineoplastic drugs on cancer cells while protecting normal cells from damage. The propargylamine modulators can be used to increase the selectivity and effectiveness of conventional antineoplastic drugs, to reduce the unwanted side-effects of cancer chemotherapy, to improve effectiveness of cancer chemotherapy and to render effective chemotherapy for previously untreatable cancers.

FIGURE 1

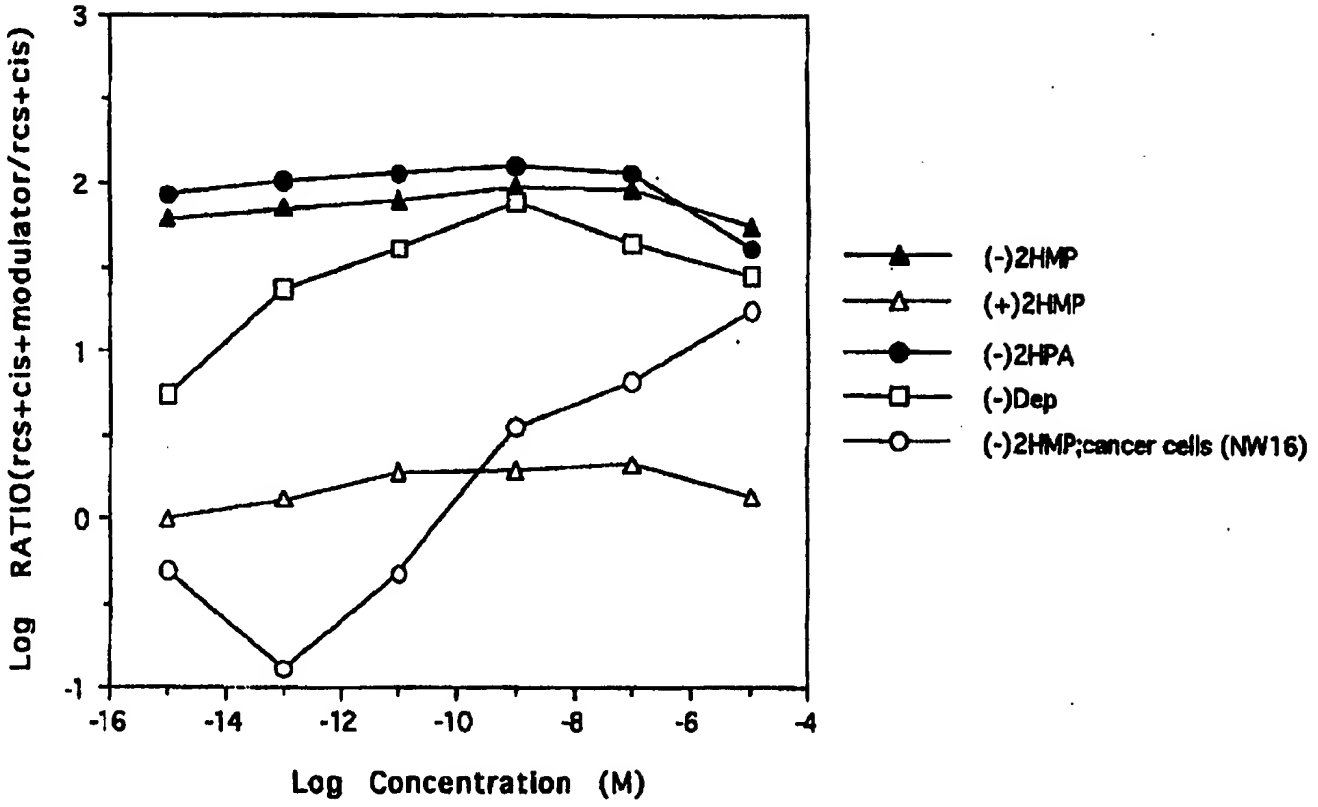


FIGURE 2

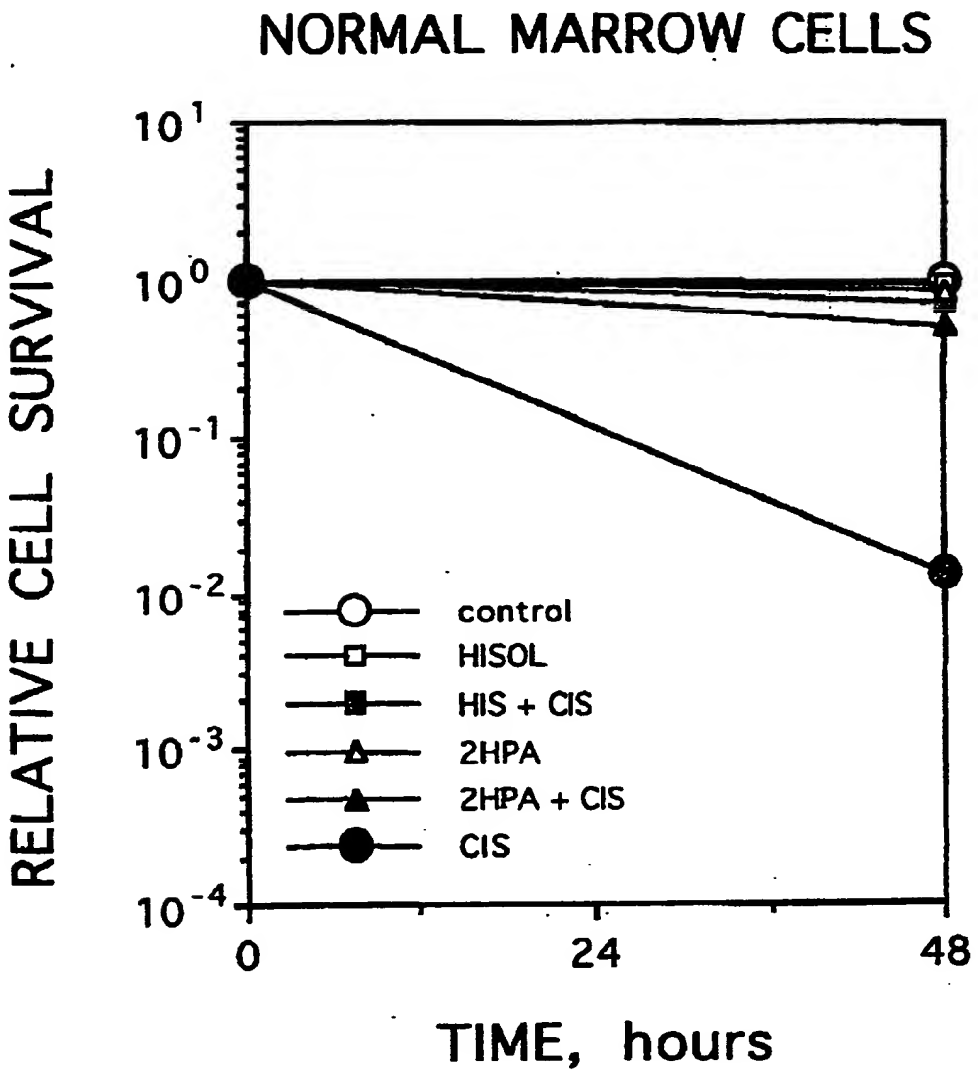
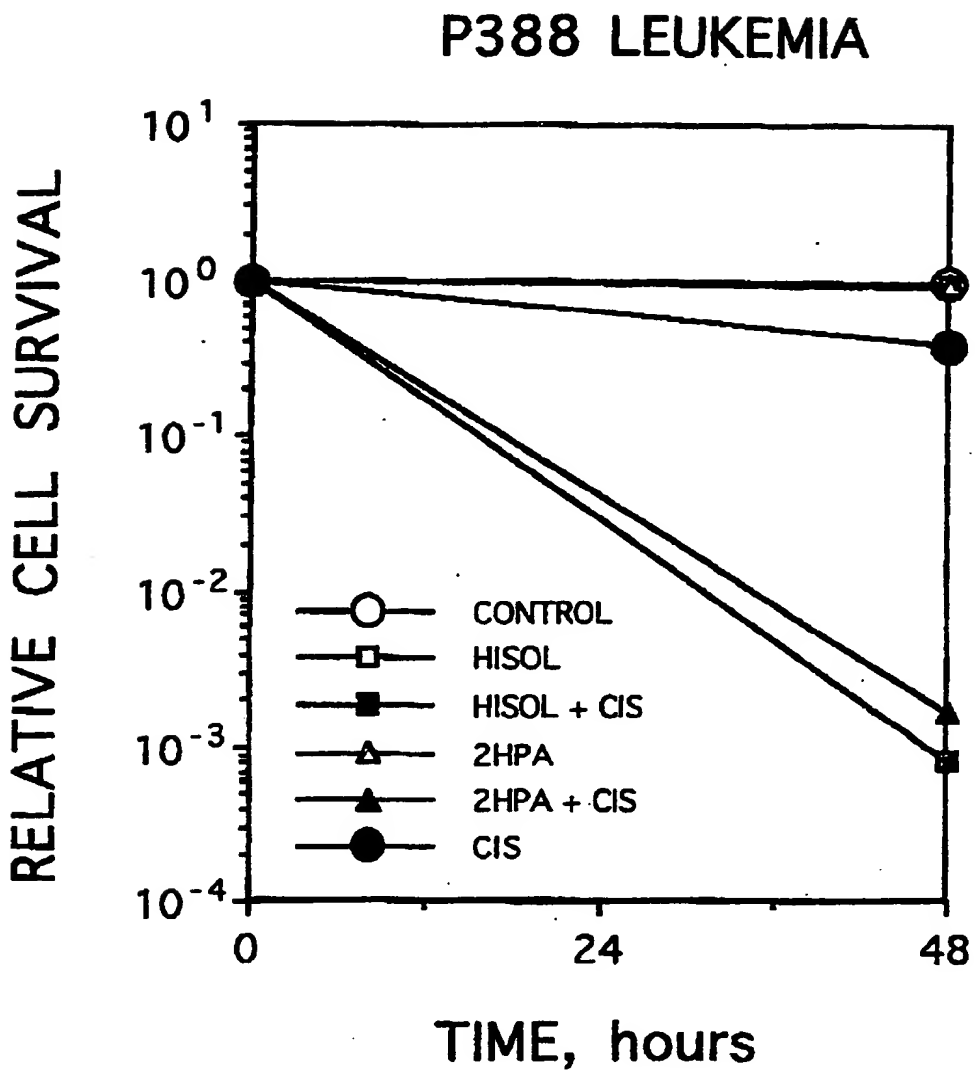

NORMAL MARROW CELLS
RELATIVE CELL SURVIVAL
10^{1}
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
control
HISOL
HIS + CIS
2HPA
2HPA + CIS
CIS
0
24
48
TIME, hours

FIGURE 3


P388 LEUKEMIA
RELATIVE CELL SURVIVAL
10^1
10^0
10^{-1}
10^{-2}
10^{-3}
10^{-4}
0
24
48
TIME, hours
CONTROL
HISOL
HISOL + CIS
2HPA
2HPA + CIS
CIS